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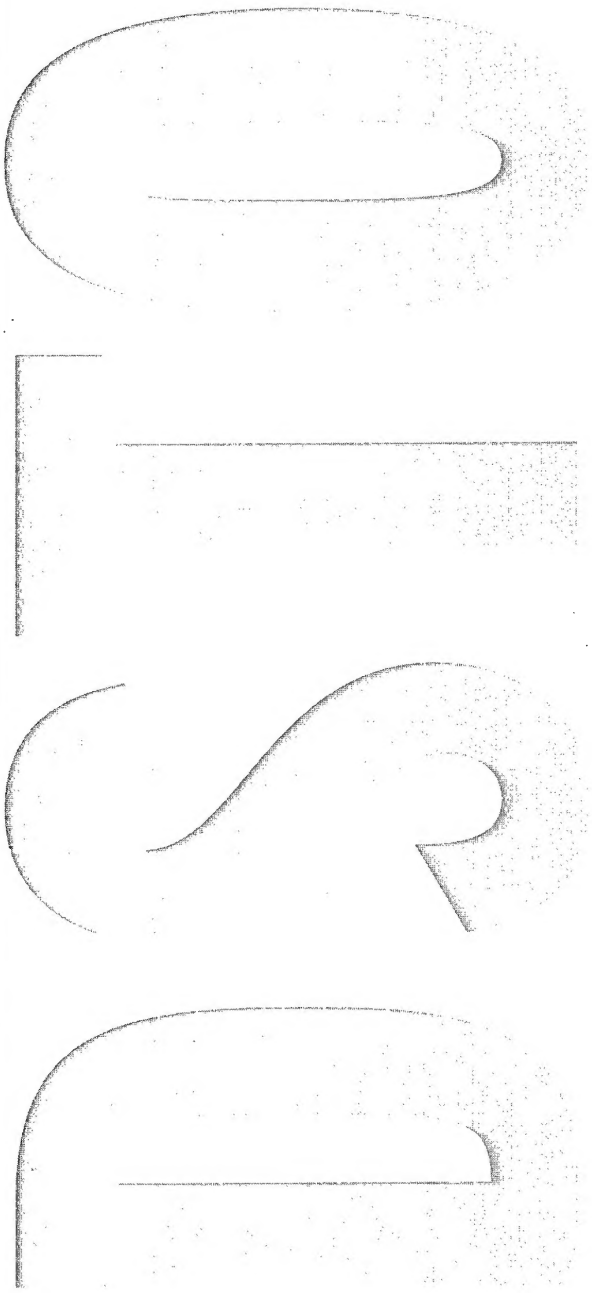

Nucleophilic Nitration of Selected Aza-aromatics: Experiments and Modelling

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and
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DSTO-TN-0389

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ABSTRACT

Nitration of isoquinoline and phthalazine has been successfully demonstrated using a novel process which does not require strong acids. In this study, nitration of isoquinoline was repeated and the method applied to 1-nitroisoquinoline and the aza-aromatics quinoline, quinazoline, quinoxaline and pyridine. Nitration of only quinoline was observed, with a product yield lower than that reported for nitration of isoquinoline. For 1-nitroisoquinoline and quinoxaline, the substrates were recovered essentially unchanged. For quinazoline and pyridine, neither the substrates nor any reaction products were isolated. In no case was multiple nitration detected. Thus, while the scope of the reaction is broader than initially reported, it is clearly not a universal method for nitrating aza-aromatics. Molecular modelling calculations have identified a correlation between the acidity of the intended nitration site and the observed yield, which might be used to screen potential substrates for this nitration technique.

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Nucleophilic Nitration of Selected Aza-aromatics: Experiments and Modelling

Executive Summary

There is an ongoing requirement for new energetic materials with enhanced performance, insensitivity and/or stability to satisfy increasingly demanding explosive and propulsion requirements of advanced weapons systems. Overwhelmingly, these materials are highly nitrated molecules, and a class of compounds which has been the target of recent evaluations is nitro-aza-aromatics. Conventional electrophilic nitration using mixed acids has limited scope and applicability for aza-aromatics due to the electronic effects of the ring-nitrogen(s), hence, considerable research effort has been directed towards alternative approaches. A novel nucleophilic method, that does not use strong acids, has been reported for nitration of isoquinoline and certain derivatives. With this method, nitration occurs adjacent to the ring-nitrogen, a result which cannot be achieved by mixed acid nitration. If this method proved to be general, it would allow synthesis of a new class of energetic materials which has the potential for enhanced performance, insensitivity and/or stability.

In this study, nitration of isoquinoline has been repeated and the method applied to 1-nitroisoquinoline and the aza-aromatics quinoline, quinazoline, quinoxaline and pyridine. Nitration only of quinoline was observed, with a product yield lower than that reported for nitration of isoquinoline. For 1-nitroisoquinoline and quinoxaline, the substrates were recovered essentially unchanged. For quinazoline and pyridine, neither the substrates nor any reaction products were isolated from the reaction. In no case was any sign of multiple nitration detected. Thus, while the scope of the reaction is broader than initially reported, it is clearly not a universal method for nitration of aza-aromatics.

"First principles" molecular modelling was used in an attempt to interpret these experimental results and to determine which aspects of the calculations can be used to predict the outcomes of relatively complex nitration chemistry. Although molecular modelling is currently incapable of yielding quantitative predictions for nitration of aza-aromatics, correlations were observed among certain reactants and nitrated products, allowing some qualitative assessments.

Contents

1. Introduction

1.1 Motivation

In order to satisfy the increasingly demanding requirements of advanced weapons systems, there is an ongoing need to develop new energetic materials with enhanced performance, better stability and less vulnerability to hazards. Overwhelmingly these materials are highly nitrated molecules, and one class of compounds targeted for further evaluation is the nitro-aza-aromatics. For these compounds, conventional nitration methods using mixed acids have limited scope and applicability due to the presence of the ring-nitrogen(s), hence considerable research effort has been expended to discover alternative approaches [1-5].

One technique has recently been reported by Baik *et al.* [6] for the nitration of isoquinoline and certain derivatives. It is a promising method for several reasons: (1) it is a mild one-step process, (2) it requires no strong acids, and (3) nitration occurs adjacent to the ring-nitrogen, a result which cannot be achieved by conventional mixed acid nitration. If this technique proves to be general, it would open up synthetic approaches to a new class of energetic materials with potential for enhanced performance, better stability and less hazards vulnerability.

Although the selection of aza-aromatics used in this study is by no means exhaustive, the experiments performed represent a considerable amount of work. The nitration process is labour-intensive, requiring careful synthetic procedures followed by time-consuming purification and characterisation of yields. In some cases - particularly for energetic materials - the resulting products can be unstable or dangerous, exposing personnel to high risk for possibly little gain. Some of this risk can be avoided by screening prospective chemicals through other means before attempting the actual experiments. Some of this screening can be done by computational chemistry with 'molecular modelling' techniques.

However, the study of energetic materials and nitrated molecules is a relatively new field in molecular modelling, and it is therefore advisable to compare computational results to existing systems before trusting model predictions of unknown systems. This study provides an excellent opportunity for testing high-level computer models for two reasons. Firstly, the motivation is simple and direct, addressing the questions:

1. Can molecular modelling be used to predict successful nitration of these selected aza-aromatics?
2. If so, which molecular models provide the best predictions?

Secondly, the nitration reaction is conceptually simple and involves relatively small molecules. Hence, several aspects of the reaction are amenable to relatively high-level calculations, thereby increasing the probability of successful prediction.

1.2 Summary of Substrates

The aromatic substrates discussed in this paper are shown in Figure 1.1 below. They are naphthalene **1**, quinoline **2**, isoquinoline **3**, pyridine **4**, cinnoline **5**, quinazoline **6**, quinoxaline **7**, and phthalazine **8**.

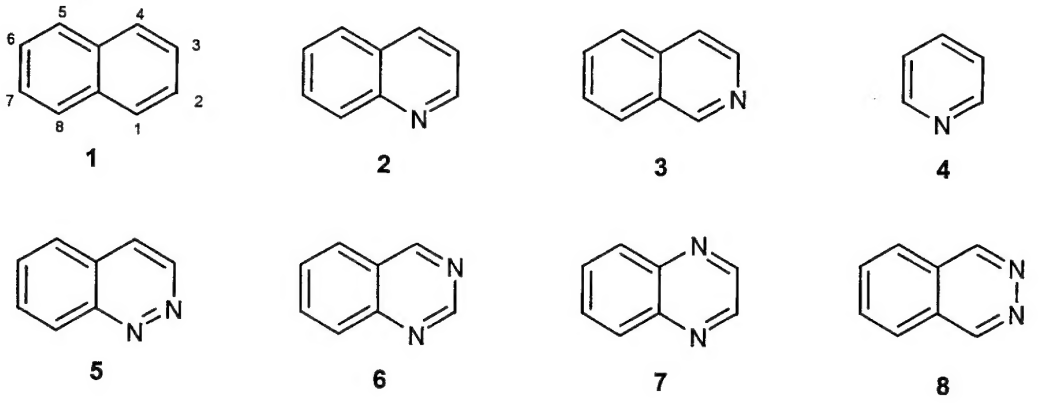


Figure 1.1. The chemical structures of selected aromatic compounds.

Experiments in this study involved reactions on the substrates quinoline **2**, isoquinoline **3**, pyridine **4**, quinazoline **6**, and quinoxaline **7**. Experimental results for the nitration of phthalazine **8** have been reported elsewhere [7] and are referenced in this paper. Molecular modelling efforts also include calculations on naphthalene **1** and cinnoline **5**. The numbering system used throughout this report to designate sites on the aza-aromatic rings is shown for naphthalene **1**.

1.3 Background

In 1996, Baik and coworkers [6] reported the successful nitration of isoquinolines at the C1 position, as shown in Figure 1.2.

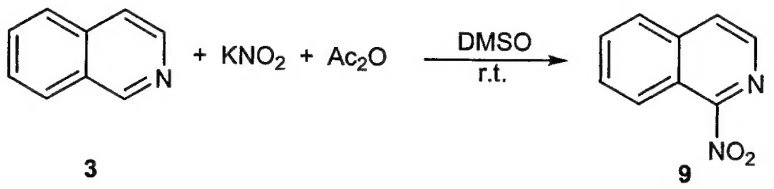


Figure 1.2. Nitration of isoquinoline.

Direct nitration at C1 had not previously been reported, although a two-step addition is possible (albeit in low yield) through successive attack by electrophilic and nucleophilic species [8]. Under normal electrophilic nitration conditions (nitric

plus sulphuric acid) substitution of isoquinoline occurs at C5 and C8 [9]. The method of Baik *et al.* is a mild, nucleophilic one-step reaction that proceeds cleanly with good to excellent yield (50 to 88%) for isoquinoline and various derivatives.

The method of Baik *et al.* for the nitration of isoquinoline involves the slow addition of acetic anhydride (Ac_2O) in dimethyl sulfoxide (DMSO) to a solution of potassium nitrite and the isoquinoline in DMSO at room temperature. Quenching of the reaction in water is followed by extraction of the product with dichloromethane and purification by chromatography and/or recrystallisation.

Through a range of experiments, Baik *et al.* determined that both the acetic anhydride and the DMSO were crucial for the reaction to proceed. From this they concluded that the method utilises a complex of DMSO and Ac_2O for electrophilic attack at the nitrogen to form an intermediate which is then susceptible to nucleophilic attack by the nitrite ion (Figure 1.3).

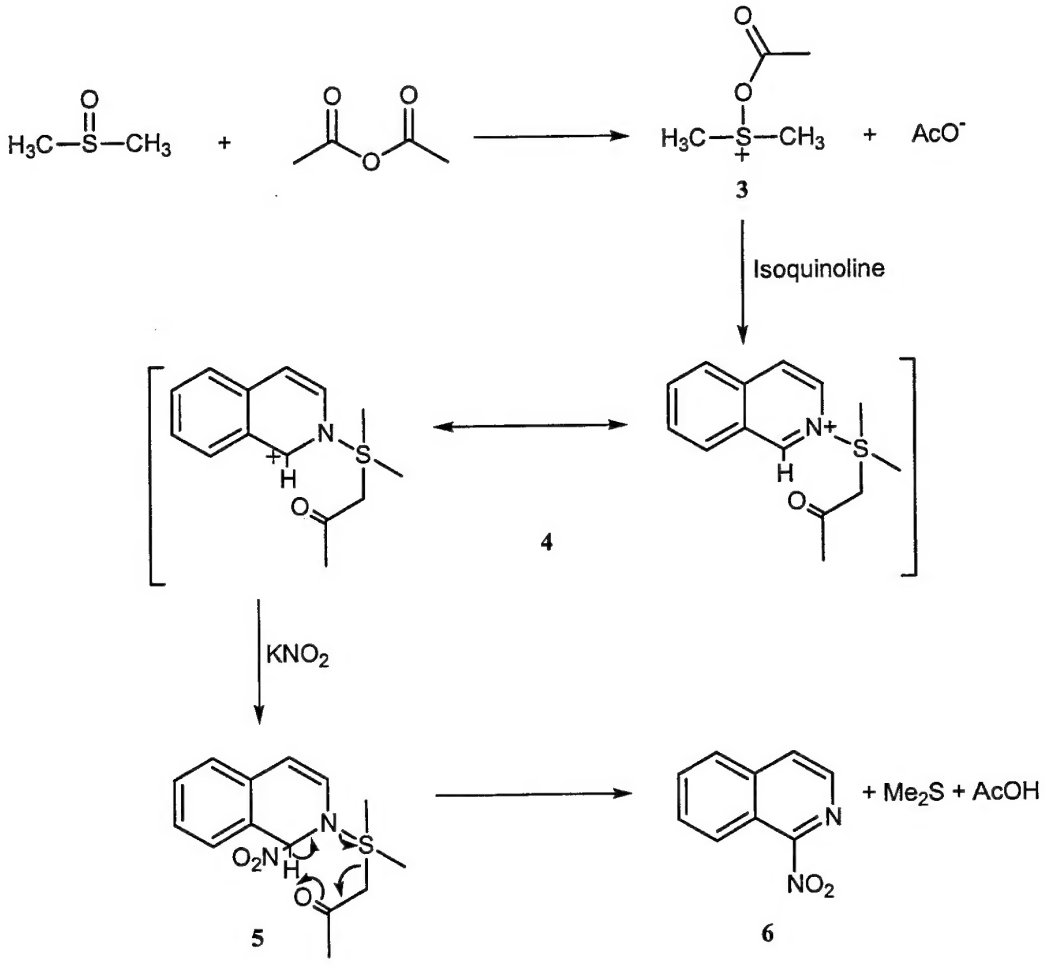


Figure 1.3. Postulated mechanism for the nitration of isoquinoline.

The introduction of substituents to different positions on the aromatic system resulted in a decreased yield, however nitration still occurred selectively at the C1 position. The lower yields were attributed to a substituent-induced increase in electron density at the C1 position inhibiting the nucleophilic addition.†

Baik and coworkers also replaced the potassium nitrite with other salts (KCN, KI and NaN_3) in an unsuccessful attempt to prepare other 1-substituted isoquinolines. They interpreted the lack of reactivity with other anions as an indication that the acidity of the C1 proton in intermediate **12** was responsible for the success of the substitution with nitrite ion.

Finally it is noted that Baik *et al.* report that the use of hexamethylphosphoramide* as a cosolvent slightly increases both the reaction rate and yield in some circumstances. Selected results are presented in Table 1.1.

Table 1.1. Published results for nitration of isoquinoline, 5-nitroisoquinoline and phthalazine using the method of Baik et al [6].

Reactant	Solvent	Time (h)	% Yield[a]	Ref.
Isoquinoline **3**, KNO_2, Ac_2O	DMSO	1	75 (23)	1
Isoquinoline **3**, KNO_2, Ac_2O	DMSO + HMPA	0.5	88 (7)	1
5-Nitroisoquinoline, KNO_2, Ac_2O	DMSO	2	51	1
Phthalazine **8**, KNO_2, Ac_2O	DMSO	2	44 (0)[b]	2

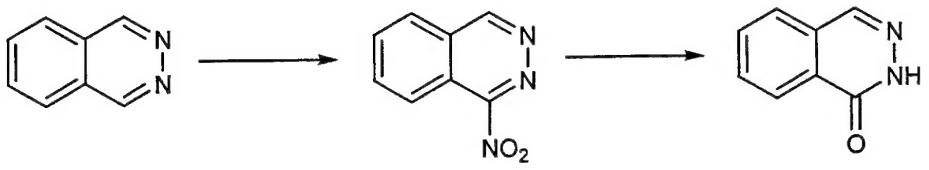
[a] *Yields in parentheses are recovered starting material*

[b] *Total reaction product was a mixture of 1-nitrophthalazine and 2H-phthalazin-1-one.*

An obvious expansion of the scope of this reaction is to use this method to nitrate other aza-aromatic systems. At the US Naval Air Weapons Center (NAWCPNS), researchers [7] attempted to nitrate phthalazine **8**. After careful workup of the crude reaction mixture, analysis by 1H NMR showed a mixture of 2H-phthalazin-1-one **14** and 1-nitrophthalazine **13.** Attempts to isolate the 1-nitrophthalazine failed with the major isolated product being **14** in 44% yield. Further studies revealed that nitro groups at the C1 position of phthalazine are susceptible to hydrolysis during isolation and purification, resulting in formation of 2*H*-phthalazin-1-one (Figure 1.4).

† This argument is not entirely convincing since a 5-nitro substituent should, if anything, lead to a *decrease* in electron density at C1, and therefore to a similar or *increased* yield of 1,5-dinitroisoquinoline. This point is discussed further in Section 4.

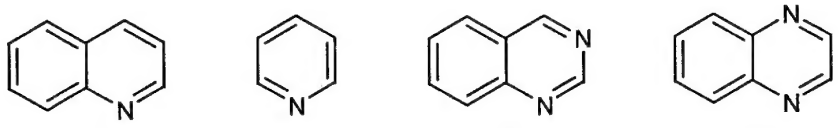
* In one section of the original paper, Baik et al refer to HMPA which is the standard abbreviation for the compound hexamethylphosphoramide, $[(CH_3)_2N]_3P(O)$. In the experimental section however they refer to the use of hexamethylphosphorous triamide $[(CH_3)_2N]_3P$, for which the standard abbreviation is HMPT. The authors of this report have judged that the compound used was most likely to be hexamethylphosphoramide.



8 13 14

Figure 1.4. Nitration of phthalazine, and hydrolysis of 1-nitrophthalazine to 2H-phthalazin-1-one.

In the current study, nitration of isoquinoline and four other aza-aromatics was attempted using the method of Baik *et al.* The additional systems chosen were quinoline **2**, pyridine **4**, quinazoline **6**, and quinoxaline **7** (Figure 1.5). Molecular modelling, in the form of *ab initio* ("first-principles") electronic structure calculations, was performed in conjunction with experiments, to assess the ability of these types of calculations to predict the success of nitration.



2 4 6 7

Figure 1.5. Aza-aromatics selected for nitration in this study.

The following sections of this technical note elaborate on the details of this study. Section 2 describes specific experimental procedures and molecular modelling calculations. Experimental results are given in section 3, followed by modelling results in section 4. Section 5 wraps up with a short discussion and conclusions.

2. Procedure

2.1 Experiment

2.1.1 Synthesis of 1-nitroisoquinoline

The conversion of isoquinoline to 1-nitroisoquinoline was carried out following the published procedure [6] (without HMPA). 1-Nitroisoquinoline was isolated in 69% yield after purification by distillation (110°C/0.5mm Hg). No attempt was made to recover any starting material.

Nitration of quinoline **2**, pyridine **4**, quinazoline **6**, and quinoxaline **7** was attempted by following the method of Baik *et al.* [6]. A variety of isolation/purification methods were trialed including distillation, recrystallisation, column

chromatography and radial chromatography, however quinoline **2** was the only compound found to undergo nucleophilic nitration (see section 2.1.1). The isolated yield of 2-nitroquinoline (12.6%) is lower than that reported for isoquinoline however no attempt was made to optimise the reaction. The experimental procedure used for this work is detailed below for the nitration of quinoline.

The reaction was repeated on 1-nitroisoquinoline to discover whether dinitration was possible by this method. Purification of the crude reaction product by column chromatography (silica, chloroform eluent) afforded only starting material in 63% recovered yield. No other identifiable products were isolated.

2.1.2 Synthesis of 2-nitroquinoline

Quinoline (0.659g) was added to a stirred solution of potassium nitrite (2.595g, 6eq.) in dimethyl sulfoxide (20mL) at ambient temperature. Acetic anhydride (3.12g, 6eq.) in dimethyl sulfoxide (22mL) was added in small portions (ca. 1mL) over 40min. A brown gas was evolved and the colour of the solution changed to brown/orange. The solution was then stirred for an additional hour. The reaction mixture was poured into water/dichloromethane (1:1, 140mL), the organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed twice with brine and dried (Na_2SO_4). Evaporation afforded a golden liquid (4.8g). Distillation (80°C/0.5mm) removed dimethyl sulfoxide; column chromatography (chloroform, silica) produced an off white solid (0.14g). Recrystallisation from ether/hexane afforded small pale yellow crystals which were identified as 2-nitroquinoline [10]. (0.112g, 12.6%), mp 128.3°C. ^{1}H NMR ($CDCl_3$) δ 7.6 – 8.1, 3H; 8.26, 1H; 8.30, 1H; 8.52, dd; 1H. ^{13}C NMR ($CDCl_3$) δ 114.28; 128.02; 130.28; 130.49; 130.75; 132.09; 141.03; 145.76; 155.17.

2.2 Modelling

Preliminary studies were performed using the PM1 semi-empirical methods available in the ChemOffice suite of programs [11]. More accurate *ab initio* or "first principles" quantum chemical calculations were then performed using molecular orbital (MO) methods available in *Gaussian98* [12] All molecules and complexes were optimised using the B3LYP density functional method with a 6-31G(d,p) basis. For more details on the application of semi-empirical or *ab initio* methods to modelling energetic materials, the reader is referred to DSTO-GD-0253 [13].

Baik *et al.* attribute the observed variation in yields of different nitration reactions to the acidity of the targeted site for nitration in different aza-aromatic compounds. One way to gauge site acidity (i.e., the ability to accept electrons) is to assign partial charges to atoms within the molecule based upon the calculated electronic structure. The conventional method for this is Mulliken population analysis [14] which estimates atomic charges from local molecular orbital densities. Although Mulliken population analysis is a somewhat arbitrary technique, it was found to be a robust

and consistent method for estimating intermolecular charges in the aza-aromatic compounds of this study.†

Mulliken population analysis was performed on Hartree-Fock (HF) molecular orbital densities. The HF method is known to be limited because it does not account for interactions between electrons (as does density functional methods like B3LYP). However, HF/6-31G(d,p) calculations were chosen over B3LYP/6-31G(d,p) because they produce better predictions for the electric dipole moments of quinoline and isoquinoline (see Table 2.1), suggesting that HF calculations more accurately reproduce intermolecular charge densities. Quoted errors for calculations are due to neglect of slight alignment corrections to the symmetry coordinates of the principle dipole (Stark) axis.

Table 2.1. Experimental and calculated electric dipole moments for quinoline and isoquinoline.

	Quinoline	Isoquinoline
Experiment [16]	2.29 ± 0.11D	2.73 ± 0.14D
HF/6-31G(d,p)	2.23 ± 0.05D	2.52 ± 0.02D
B3LYP/6-31G(d,p)	2.00 ± 0.05D	2.37 ± 0.02D

For molecular modelling results presented below, quoted values for Mulliken charges include contributions from both the heavy atom (C or N) and any bonded hydrogens.

Quoted binding energies for reaction intermediates were obtained by subtracting the energies of the $[S(CH_3)_2CCH_3O_2]^+$ ligand and the aza-aromatic substrate from the total energy of the system. Thus for the isoquinoline complex, the binding energy is given by:

$$E_b = E_{isoquinoline\ complex} - E_{isoquinoline} - E_{[S(CH3)2CCH3O2]+}$$

Given the qualitative nature of this study, no attempt was made to include zero-point energies or counterpoise corrections in the calculations.

† A more consistent method for estimating intermolecular charges – "atoms in molecules" or AIM [10] - is based upon an analysis of the calculated local electronic charge density (as opposed to MO densities). AIM calculations for the isoquinoline reaction intermediates failed to converge.

3. Results and Discussion: Experimental

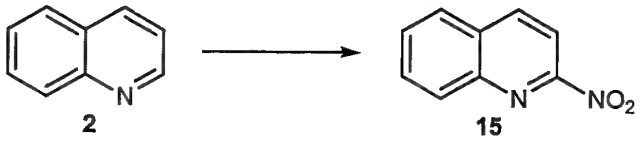
The results of the attempted nitration of isoquinoline, quinoline, quinazoline, quinoxaline and pyridine by the method of Baik *et al.* are summarised in Table 3.1.

Table 3.1. Experimental results for the attempted nitration of selected aza-aromatics

Reactant	Solvent	Product	% Yield[a,b]
Isoquinoline **3**, KNO_2, Ac_2O	DMSO	2-nitroisoquinoline **14**	69 (0)
Quinoline **2**, KNO_2, Ac_2O	DMSO	2-nitroquinoline **14**	12.6 (0)
Pyridine **4**, KNO_2, Ac_2O	DMSO	-	(0)
Quinazoline **6**, KNO_2, Ac_2O	DMSO	quinazoline derivative[c]	~ 5 (0)
Quinazoline **6**, KNO_2, Ac_2O	DMSO + HMPA	-	0 (0)
Quinoxaline **7**, KNO_2, Ac_2O	DMSO	-	(91)
Nitroisoquinoline **9**, KNO_2, Ac_2O	DMSO	-	(>75)

[a] *Yields in parentheses are recovered starting material*
[b] *Yields are not optimised.*
[c] *Unidentified crude product, not reproducible.*

The only compound for which the targeted nitration was successful was isoquinoline, as reported by Baik *et al.*, and quinoline (Figure 3.1).



2 **15**

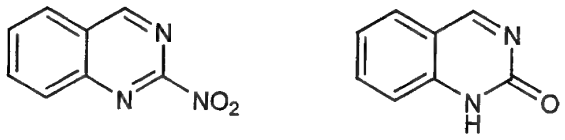
Figure 3.1. Nitration of quinoline via the method of Baik et al.

For quinoxaline, almost all of the starting material was recovered, indicating that very little reaction, if any, occurred.

For pyridine and quinazoline, the lack of identifiable product or recovered starting material could have two possible explanations:

1. The starting materials (unlike isoquinoline) are water soluble and would be lost during the aqueous workup.
2. Reactions occurred which led to non-isolable products.

For quinazoline, a small amount of a crude compound was isolated from one attempt at nitration. NMR and mass spectral analysis clearly showed that whilst it was a quinazoline derivative it was neither the desired 2-nitroquinazoline **16** or a hydrolysis product **17** similar to that observed by NAWCWPNS researchers for the nitration of phthalazine. This unidentified product was not isolated during repetitions of this reaction, even when HMPA was used as a co-solvent.



16 17

Figure 3.2. Potential products from the quinazoline nitration.

Finally, an attempt was made to nitrate 1-nitroisoquinoline **9** (Figure 3.3). No indication of further nitration was observed, and the bulk of the starting material was recovered. This result could be expected from steric considerations, since the 1-nitro substituent would hinder the formation and correct orientation of the reaction intermediate analogous to **11**.

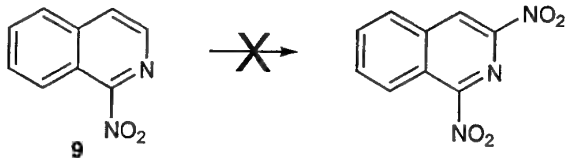


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Figure 3.3. Attempted nitration of 1-nitroisoquinoline via the method of Baik et al.

4. Results and Discussion: Modelling

4.1 Background

For isoquinoline **3**, early calculations [16, 17] indicate that the C1 site has the lowest π-electron density (highest proton acidity), and should therefore be preferred for nucleophilic reaction. Semi-empirical calculations support two more conclusions:

1. The hypothetical intermediate complex **11** in Figure 1.4 is stable. It is therefore reasonable to assume that the subsequent reactions (*i.e.*, attachment of the nitro ion and subsequent breakup of the complex) also occur as outlined by Baik *et al.*
2. Double nitration of isoquinoline is sterically hindered – that is, the nitro group in 1-nitroisoquinoline **9** interferes with free rotation of the $[S(CH_3)_2CCH_3O_2]^+$ ligand, preventing correct orientation for nitration/ deprotonation of the C5 site. By the same argument, only one nitration can occur for quinazoline **6**.

For *ab initio* calculations, the modelling falls naturally into three parts associated with (1) the reactant, (2) the intermediate complex and (3) the nitrated products. Studies of the substrate can determine which ring carbons of the aza-aromatics are most susceptible to nucleophilic attack. Studies of the intermediate complex yield

optimal structures and binding energies, and lend some insight as to how the complex assists nitration. Finally, studies of the nitrated products may lead to correlating structural characteristics with tendencies towards further reaction (*eg.*, hydrolysis).

4.2 Reactants

4.2.1 Energetics

The calculated total energies of the reactants are listed in Table 4.1. These energies provide an indicator of the relative stabilities of the intermediate complexes and the nitrated products. Basis set effects are not taken into account, so errors associated with absolute energies are expected to average around 0.015 au (10 kcal mol^{-1}), but could exceed 0.03 au (20 kcal mol^{-1}).

Table 4.1. B3LYP/6-31G(d,p) total energies for reactants

Reactant	Total Energy (au)
$[NO_2]^-$ ion	-205.1203864
$[S(CH_3)_2CCH_3O_2]^+$ ligand	-706.2206657
Quinoline **2**	-401.9416561
Isoquinoline **3**	-401.9398502
5-methoxyisoquinoline	-516.4655806
5-nitroisoquinoline	-606.4327559
Pyridine **4**	-248.2926053
Cinnoline **5**	-417.9414160
Quinazoline **6**	-417.9790704
Quinoxaline **7**	-417.9741550
Phthalazine **8**	-417.9433838

4.2.2 Mulliken charges

The most likely site for nucleophilic nitration of an aza-aromatic molecule is the ring carbon with the lowest π-electron density. The simplest way to represent the magnitude of local electron density at a particular site is by assigning a partial electrostatic charge to that site. Table 4.2 lists assigned partial charges of all ring atoms in the reactants, based upon Mulliken population analysis. Comparison of the aza-aromatic molecules with naphthalene shows that nitrogen strongly perturbs the electronic structure of the ring, drawing electron density from adjacent sites. Hence, nearby ring carbons have a large positive Mulliken charge. Based upon this analysis, the preferred sites for nucleophilic substitution in the non-symmetric aza-aromatics is C2 for quinoline, C1 for isoquinoline, C3 for cinnoline, and C2 for quinazoline.

Table 4.2. Mulliken charges assigned to ring atoms selected aromatic molecules.

Compound	1	2	3	4	5	6	7	8
Naphthalene **1**	0.02	-0.01	-0.01	0.02	0.02	-0.01	-0.01	0.02
Quinoline **2**	N	0.29	-0.06	0.10	0.02	-0.00	0.00	0.05
Isoquinoline **3**	0.31	N	0.26	-0.03	-0.02	0.02	-0.01	0.04
Pyridine[a]**4**	N	0.28	-0.05	0.07	-0.05	.28	–	–
Cinnoline **5**	N	N	0.23	0.05	0.03	0.02	0.00	0.09
Quinazoline **6**	N	0.49	N	0.36	0.05	-0.01	0.03	0.04
Quinoxaline **7**	N	0.24	0.24	N	0.05	0.01	0.01	0.05
Phthalazine **8**	0.29	N	N	0.29	0.05	0.02	0.02	0.05

[a] *For pyridine, numbering of the carbons continues around the single ring.*

4.3 Reaction Intermediates

4.3.1 The isoquinoline complex

Preliminary calculations for the reaction intermediates were performed with isoquinoline, to assess the feasibility of forming the molecular complex **11** proposed by Baik and coworkers.

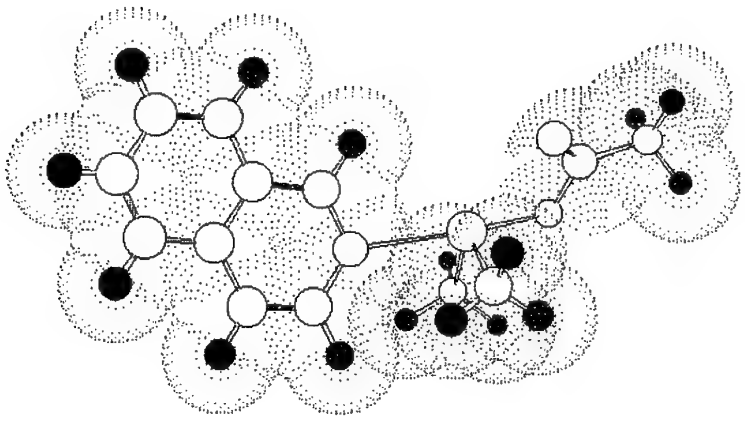

Figure 4.1. The optimum structure of the isoquinoline-$S(CH_3)_2CCH_3O_2$ reaction intermediate (C1 complex).

The optimum structure of the reaction intermediate for isoquinoline nitration is shown in Figure 4.1, and has a B3LYP/6-31G** binding energy of 23 kcal/mol. Attachment of the $[S(CH_3)_2CCH_3O_2]^+$ ligand causes only minor changes in the isoquinoline with the ring structure remaining planar. The predicted distance between the isoquinoline and complex (S-N bond length) is 2.41Å, with the S and carboxyl O atoms located in the plane of the isoquinoline (∠N-S-O = 176°). The carbonyl O lies slightly above the molecular plane (∠C1-C2-C3-O = 20°) and 3.97Å

from the C1 hydrogen. The hydrogens of the sulfur methyl groups are approximately 2.5 Å from the C3 hydrogen, with $\angle CH_3\text{-}S\text{-}CH_3 = 103°$.

An alternative orientation of the intermediate complex is to have the carbonyl oxygen of the ligand pointing to the C3 hydrogen. The predicted binding energy of this system, 22 kcal/mol, is only slightly less than that of the optimal structure, indicating that there should be no orientationally preferred structure at standard temperatures and pressures. This suggests that the observed preference for nitration at the C1 position is more likely due to chemical changes in the isoquinoline than to the structure of the reaction intermediate.

Vibrational analysis of the isoquinoline complex indicates that the S-N bond is extremely flexible. Zero-point motion contributes nearly 180 kcal/mol of energy to the bound complex, with at least 12 vibrational modes activated at room temperature. Among these activated vibrations, torsional and bending modes about the S-N bond result in large contortions of the system away from the optimum structure. It is therefore unlikely that small shifts in binding energies or structural properties significantly modify the ability of the complex to assist nitration, and that electronic effects (e.g., proton acidity) are more important.

Calculated atomic charges for the complex differ somewhat from those proposed by Baik *et al.* Whereas they assign a positive charge to the isoquinoline nitrogen, Mulliken population analysis predicts a negative charge, and assigns most of the positive charge to the $[S(CH_3)_2CCH_3O_2]^+$ ligand†, so that $q_{isoquinoline} = +0.12e$ and $q_{Sgroup} = +0.88e$. However, Mulliken population analysis predicts a 'pocket' of positive charge around the C1 site, which should be highly attractive to an approaching nitrite anion.

Table 4.3 lists binding energies for the two possible isoquinoline complexes along with Mulliken charges for pertinent ring atoms in each system. Calculations predict that formation of the intermediate complex increases the positive charge (*i.e.*, the acidity) of both C1 and C3. Interestingly, C1 is predicted to be the most acidic site, regardless of where the active end of the ligand (the carbonyl oxygen) is pointed.

Also included in Table 4.3 are Mulliken charges for 5-nitroisoquinoline and 5-methoxyisoquinoline. These compounds were successfully nitrated in the original study by Baik *et al.*, but with lower yields than isoquinoline. Their explanation for the reduced yield - that the substituents increase the electron density at C1 - contradicts modelling results, which predict a similar or lower electron density (higher site acidity) for the substituted isoquinolines and their associated reaction intermediates. Hence, if nitration yield does correspond to target site acidity, it cannot be predicted by a simple proportional relationship.

† Specifically, the nitrogen has a Mulliken charge $q_N = -0.76e$ and the sulfur, $q_S = +1.03e$.

Table 4.3. Mulliken charges of ring atoms of isoquinoline species throughout the nitration reaction.

System[a]	Total Energy (au)	E_b (kcal/mol)	C1	N2	C3	C4
Isoquinoline **3**	-401.9398502	--	0.31	-0.55	0.26	-0.03
N2/C1 complex	-1108.1967845	-22.8	0.42	-0.76	0.30	-0.01
N2/C3 complex	-1108.1959598	-22.2	0.39	-0.75	0.33	0.01
5 Nitroisoquinoline	-606.4327559	--	0.33	-0.55	0.29	0.05
N2/C1 complex	-1312.6808305	-17.2	0.42	-0.74	0.31	0.09
5-Methoxyisoquinoline	-516.4655806	--	0.30	-0.55	0.25	0.02
N2/C1 complex	-1222.7259615	-24.9	0.42	-0.76	0.29	0.07

[a] Complexes are designated by the bonding nitrogen and the ring carbon closest to the active end of the ligand.

4.3.2 Reaction intermediates of the other aza-aromatic compounds

All the aza-aromatics in this study are predicted to form stable intermediate complexes analogous to that proposed by Baik *et al.* for isoquinoline. Calculated binding energies for the complexes range from 15 to 30 kcal/mol and are listed in Table 4.4.

Table 4.4. B3LYP/6-31G(d,p) binding energies for all reaction intermediates.

System[a]	Total Energy (au)	ΔE (kcal mol^{-1})
Quinoline **2** complex	-1108.1944356	-20.2
Pyridine **4** complex	-954.5454035	-20.2
Cinnoline **5** complex	-1124.2074618	-28.5
Quinazoline **6**		
N2/C1 complex	-1124.2292529	-18.5
N2/C3 complex	-1124.2279816	-17.7
N4/C3 complex	-1124.2261014	-16.5
Quinoxaline **7** complex	-1124.2192182	-15.3
Phthalazine **8** complex	-1124.2120671	-30.1

[a] Systems that can form more than one complex structure unrelated by symmetry are designated by the nitrogen to which the ligand is bound, and the ring carbon targeted for nitration.

As with isoquinoline, formation of the reaction intermediate causes very little distortion of the aza-aromatic substrate. Similarly, the structure of the $[S(CH_3)_2CCH_3O_2]^+$ ligand remains relatively constant over the range of complexes studied. Given the relatively flexible S-N bond, the most notable structural differences among the reaction intermediates involved the atomic angles and distances that define the active region of the complex. These bond lengths and angles are given in Table 4.5.

Table 4.5. Pertinent structural parameters within the 'active region' of optimised reaction intermediates.

Complex	S-N length (Å)	∠C-N-S (°)	H...O length (Å)
quinoline **2** complex	2.52	103.4	3.76
isoquinoline **3**			
N2/C1 complex	2.41	109.6	3.97
N2/C3 complex	2.44	108.5	3.95
pyridine **4** complex	2.41	109.8	3.94
cinnoline **5** complex	2.46	120.0	4.45
quinazoline **6**			
N2/C3-complex	2.62	103.3	3.85
N2/C1-complex	2.50	110.0	4.01
N4/C3-complex	2.55	107.9	4.01
quinoxaline **7**	2.62	103.7	3.82
phthalazine **8**	2.44	121.6	4.48

Of the aza-aromatics studied, only three are known to undergo nucleophilic nitration: quinoline, isoquinoline and phthalazine. Optimised structures of the reaction intermediates show substantial differences between the active regions of these three compounds. This suggests there is little correlation between the most stable structure of the reaction intermediate and the likelihood of nitration. Since the complex is subject to large distortions due to thermal motion and electrostatic interaction with the approaching $[NO_2]^-$ anion, this could be expected.

As with isoquinoline, formation of the reaction intermediate changes the distribution of electron density within the aza-aromatic molecule, particularly for ring sites adjacent to the S-N bond. Charge assignments for pertinent ring atoms within each reactant and complex are listed in Table 4.6. Notably for quinazoline, the C2 site is more acidic than the C4 site regardless of the orientation of the complex.

Table 4.6 Mulliken charges for pertinent ring atoms of reactants and intermediate complexes.

System	1	2	3	4	5	6
quinoline **2**	N	0.29	-0.06	0.10	--	--
N1/C2-complex	N	0.38	-0.04	0.17	--	--
pyridine **4**	N	0.28	-0.05	0.07	-0.05	0.28
N1/C2-complex	N	0.36	-0.00	0.14	-0.01	0.33
cinnoline **5**	N	N	0.23	0.05	--	--
N2/C3-complex	N	N	0.31	0.09	--	--
quinazoline **6**	N	0.49	N	0.36	--	--
N2/C3-complex	N	0.53	N	0.45	--	--
N2/C1-complex	N	0.55	N	0.41	--	--
N4/C3-complex	N	0.57	N	0.43	--	--
quinoxaline **7**	N	0.24	0.24	N	--	--
N1/C2-complex	N	0.32	0.28	N	--	--
phthalazine **8**	0.29	N	N	0.29	--	--
N2/C1-complex	0.42	N	N	0.37	--	--

4.4 Nitration products

Calculated total energies of the targeted nitrated aza-aromatic products are given in Table 4.7, along with predicted reaction energies and selected structural parameters.

Table 4.7. Calculated total energies, reaction energies and structural distortion parameters[a] of nitrated aza-aromatics.

System	E (au)	$\Delta E_{nitration}$ (kcal/mol)	a	b	c	d	e	NO_2 'twist'
2-nitroquinoline	-606.4382342	+391.4	0.0	0.0	0.0	0.0	0.0	0.0
1-nitroisoquinoline	-606.4292266	+396.0	0.0	0.0	0.0	0.0	0.0	0.0
2-nitropyridine	-452.7884832	+391.9	0.0	--	0.0	--	--	0.0
3-nitrocinnoline	-622.4334415	+394.3	0.0	0.0	0.0	0.0	0.0	0.0
2-nitroquinazoline	-622.4689017	+395.7	0.0	0.0	0.9	1.1	0.0	31.6
4-nitroquinazoline	-622.4676063	+396.5	1.8	0.3	0.6	0.5	1.3	43.2
2-nitroquinoxaline	-622.4672049	+393.7	0.0	0.0	0.0	0.0	0.0	0.0
1-nitrophthalazine	-622.4310581	+397.0	1.7	0.2	0.6	0.8	1.3	42.0
1,4 dinitrophthalazine	-826.9138921	+400.1	3.7	0.3	1.6	1.6	1.6	46.8
1,5-dinitroisoquinoline	-810.9203943	+397.1	1.0	0.6	0.7	1.0	1.0	45.1
1-nitro 5-methoxy-isoquinoline	-720.9572832	+394.5	1.6	0.2	1.0	0.2	1.3	41.3

[a] Ring distortions are quantified in terms of the dihedral angles described in Figure 4.2.

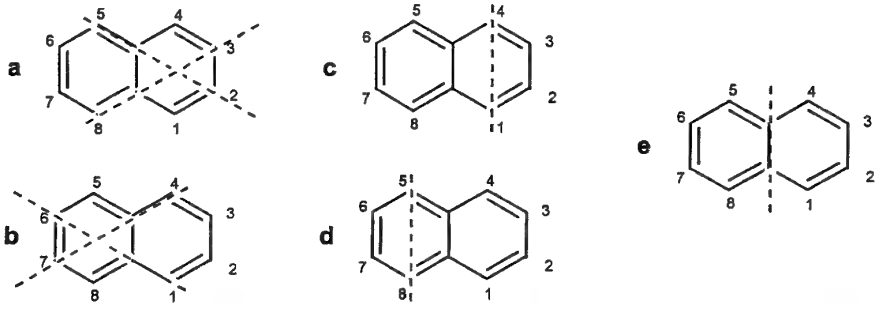

Figure 4.2 Classification of ring distortions observed in aza-aromatics. Quantities recorded in Table 4.7 refer to the magnitude of dihedral angles described by the folding axes (dashed lines).

As mentioned in the introduction, although phthalazine can be nitrated via the method of Baik *et al.*, NAWCWPNS researchers [7] found that the product was subject to further hydrolysis reactions in the aqueous workup and purification procedures. The optimum structure of 1-nitrophthalazine is non-planar, with ring distortion and a nitro group twisted along the C-N axis, pushing the nitro oxygens out of the plane of the molecule. Hence calculations were conducted to determine whether the stability of the product can be correlated to out-of-plane distortion in the optimum structures. The various ring distortions of 1-nitrophthalazine may be described in terms of particular dihedral angles, as shown in Figure 4.2; these

dihedral angles were calculated for all the nitration products and listed in Table 4.7. Although miscellaneous products were detected after attempted nitration of phthalazine and quinazoline, no other reaction products were reported by Baik *et al.* for nitration of 5-nitroisoquinoline or 5-methoxyisolquinoline, indicating there is no simple correlation between reaction stability and ring distortion of nitrated products.

NAWCWPNS researchers were able to identify the presence of 1-nitrophthalazine by reducing exposure of the product to aqueous conditions. However, they did not detect formation of dinitrophthalazine. Based upon considerations of proton acidity, the reaction should continue since the targeted site in nitrophthalazine has a higher Mulliken charge than phthalazine in both the substrates (0.34*e* vs 0.29*e*) and the reaction intermediates (0.50*e* vs 0.42*e*). Nor can reaction progress be explained in terms of steric effects, since the nitro group does not inhibit formation of the reaction intermediate. Indeed, the predicted structure of the nitrophthalazine complex is similar to those listed in Table 4.5, and has a binding energy of 23.4 kcal/mol. It is also unlikely that complexation causes hydrolysis, since attachment of the ligand *reduces* distortion of the optimum structure (*eg.*, dihedral **a** relaxes from 1.7° to 0.6°, and nitro torsion decreases from 42° to 39°). However, the predicted structure for dinitrophthalazine has more out-of-plane distortion than nitrophthalazine. If the correlation between molecular stability and ring distortion can be extrapolated to this case, then dinitrophthalazine is less stable than nitrophthalazine.

5. Conclusions

The experimental component of this study has shown that nitration via the method of Baik *et al.* is not widely applicable to aza-aromatic systems beyond the scope of the original study. This is consistent with the proposed mechanistic pathway (Figure 1.4) which indicates that the reaction would be highly susceptible to electronic influences as well as being limited by a crowded steric environment.

First-principles molecular modelling predictions support the reaction mechanism proposed by Baik *et al.* for nucleophilic nitration of isoquinoline: the reaction intermediate is stable and the targeted site for nitration becomes more acidic upon formation of the complex. Less successful, however, were attempts to qualitatively predict which of selected aza-aromatics could be nitrated via this method. Structural analyses of reaction intermediates and products were inconclusive; this could be expected since:

1. the reaction intermediate is very flexible and therefore subject to large distortions under thermal motion at room temperatures; and
2. the amount of product retrieved in the experiment could be due to other factors (*eg.*, water solubility).

Some correlations were noted between observed product yields and calculated acidities for targeted nitration sites on the substrate ring structures. Simple Mulliken population analysis of local electron densities consistently predicted likely sites for nucleophilic substitution.† There is also some correlation between the acidity of the target site and the observed product yield, as shown in Figure 5.1. As proposed by Baik and coworkers, the yield increases with increasing site acidity up to a point. With nitro and methoxy substituted isoquinolines, Baik *et al.* reported a decreased yield which they attributed to a reduction of site acidity. However, calculations in this study predict a higher site acidity. A possible explanation, suggested by Table 5.1, is that there is a threshold value for proton acidity below which no reaction occurs. If this relationship holds true for all the compounds listed, then the calculations predict that the method of Baik *et al.* will not nitrate cinnoline, an aza-aromatic molecule which has yet to be tested.

Table 5.1 Observed product yields and calculated target proton acidities (Mulliken charges) for nucleophilic nitration of selected aza-aromatic compounds.

System	Proton charge (e)	Nitration yield (%)
cinnoline **5**	0.309	–
quinoxaline **6**	0.318	0
pyridine **4**	0.363	–
quinoline **2**	0.380	13 (unoptimised)
isoquinoline **3**	0.388	88
phthalazine **8**	0.410	44
5-methoxyisoquinoline	0.419	57
5-nitroisoquinoline	0.424	51

Generally, the predictions of first-principles electronic structure models can be improved with more sophisticated calculations, including:

1. a model of the reaction path which includes the approach of the $[NO_2]^-$ anion;
2. a more sophisticated analysis of electronic structure;
3. systematic analysis of thermal properties;
4. inclusion of solvent effects.

Of these improvements, only the first - modelling the approach of the $[NO_2]^-$ anion - was attempted, but preliminary work involved very time-consuming calculations, and led to no further insights. The other improvements are also expected to yield little gain at substantial computational expense. Given this and the corresponding lack of experimental success, no further studies were attempted.

† Mulliken population analysis failed, however, to consistently predict the converse, that is, which sites are most likely to undergo *electrophilic* substitution – the more conventional approach to nitrating organic molecules.

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19. ABSTRACT

Nitration of isoquinoline and phthalazine has been successfully demonstrated using a novel process which does not require strong acids. In this study, nitration of isoquinoline was repeated and the method applied to 1-nitroisoquinoline and the aza-aromatics quinoline, quinazoline, quinoxaline and pyridine. Nitration of only quinoline was observed, with a product yield lower than that reported for nitration of isoquinoline. For 1-nitroisoquinoline and quinoxaline, the substrates were recovered essentially unchanged. For quinazoline and pyridine, neither the substrates nor any reaction products were isolated. In no case was multiple nitration detected. Thus, while the scope of the reaction is broader than initially reported, it is clearly not a universal method for nitrating aza-aromatics. Molecular modelling calculations have identified a correlation between the acidity of the intended nitration site and the observed yield, which might be used to screen potential substrates for this nitration technique.

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